REMARKS

Applicants reply to the Examiner's comments in the Advisory Action mailed on July 19, 2006. Applicants request that the Examiner enter the above amendments and consider the following remarks prior to examining the above-referenced patent application after RCE. Claims 1, 2, 4, 6-10 and 14-17 were pending in the application. Applicants cancel claim 2 without prejudice to filing other applications with one or more claims having similar subject matter. Applicants add new claims 43-59. Support for the amendments may be found in the originally-filed specification, claims, and figures. No new matter has been introduced by these amendments. Reconsideration of this application is respectfully requested.

Support for Amendments

Applicants amend independent claims 1 and 17 to recite "a live cell to maintain the biological activity of the live cell." Support for "live cell" can be found on, for example, page 18, lines 12-17 and page 73, lines 30-32 of the originally filed specification. Page 18, lines 12-17 states:

> "The term 'cell' herein is used in its broadest sense in the art, referring to a structural unit of tissue of a multicellular organism, which is capable of self replicating, has genetic information and a mechanism for expressing it, and is surrounded by a membrane structure which isolates the living body from the outside."

Page 73, lines 30-32 states:

> "This method is based on the principle that live (viable) cells do not take up certain dyes, whereas dead (non-viable) cells do."

Support for the terms "biological activity" and "maintain biological activity" can be found in, for example, claim 2 and from page 31, lines 25-30 and page 32, lines 13-18 of the originally filed specification. Original claim 2 states:

> "2. A method accordingly to claim 1, wherein the predetermined range of velocity maintains a biological activity of the cell."

Page 31, lines 25-30 states:

> "As used herein, the term 'biological activity' refers to activity possessed by an element (e.g., a polynucleotide, a protein, etc.) within an organism, including activities exhibiting various functions (e.g., transcription promoting activity,

proliferation activity, cell division activity, etc.). For example, when two elements interact with each other, the biological activity includes binding of the two molecules and a biological change due to the binding."

Page 32, lines 13-18 states:

"As used herein, the term 'maintain biological activity' in relation to a biological material, means that at least one type of biological activity as defined above of the biological material is maintained at at least about 50% compared to the biological activity when the biological material was prepared."

Applicants amend claim 17 to recite "A method for treating ~~an organ~~ a subject in need thereof". Support for this amendment can be found on, for example, page 24, lines 19-20 in the originally filed specification. Page 34, lines 19-20 states:

"The present invention provides a method fox effectively administering a biological material to a subject,"

Applicants add new claims 43-59. Support for new claims 43-45 and 56-58 can be found on, for example, page 80, lines 8-13, and support for claims 47-55 can be found in original claims 3-16. Page 80, lines 8-13 states:

"To be summarized, it was found that cells are not substantially damaged if the velocity range thereof is about 20 ml(/min) or less, In addition, it was found that the proliferation rate of a cell is not affected if the velocity is less than about 10 ml/min."

Support for claims 46 and 59 can be found in, for example, page 13, line 23 to page 14, line 5. Page 13, line 23 to page 14, line 5 states:

"Thus, the invention described herein makes possible the advantages of providing (1) a method and system for injecting a liquid drug containing a biological material, such as a gene, a cell, or the like, into organisms efficiently and effectively while maintaining a velocity and/or acceleration thereof unchanged, without damaging the biological material, thereby making it possible to expect significant improvement in the therapeutic effect of cell implantation therapy, (2) a device for injecting a liquid drug into the body while maintaining a predetermined velocity and/or acceleration unchanged, whereby, for example, when a cell-containing liquid is injected into the body, it is possible to suppress

the adverse influence of injection pressure on a cell, and (3) a liquid drug injecting device having a simple structure suitable for injection of a cell-containing liquid into the body"

Comments Regarding the Cited References

The Examiner maintains his rejection of pending claims 1-4, 6-13, 16 and 17 under 35 USC 103 as being obvious over WO 99/39624 ('624) in view of US 6,673,604 ('604). The Examiner also maintains his rejection of pending claims 12, 13, 16 and 17 as being obvious over US 5,690,618 ('618) in view of '604. Applicants respectfully traverse these rejections.

Applicants assert that the '618 reference teaches an electronic syringe in which the flow rate and acceleration/deceleration patterns can be altered. For example, at column 8, lines 45-54 it states:

> "The computer could verify based on the information available, whether the patient is sensitive to the anesthetic selected and offer alternatives,, Should the patient record indicate any other special requirements for example, patient history with respect to pain thresholds, the computer would then load syringe 10 with data representing a predetermined operating sequence. Such an operating sequence may include acceleration/deceleration patterns, flow rate data and amount of anesthetic to administer."

Column 6, lines 14-21 states:

> "In development of the present electronic syringe, it has been determined that the patients suffer the most discomfort when injection fluid enters the tissue. The patient will also experience pain if the flow rate of anaesthetic entering the tissue is too fast. It has been determined that typical injections take from 15 seconds to 45 seconds to administer approximately 1.8 ml of anaesthetic depending on the size of the needle diameter employed."

The '618 reference only teaches altering the parameters of flow rate, acceleration and deceleration to reduce patient discomfort when injection fluid enters the tissue (column 6, lines 15-16), but not to maintain the biological activity of an injected cell by preventing cell damage by controlling of velocity. In other words, the controlling of velocity in order to maintain biological activity of an injected cell is not taught by the '618 reference. Further, '618 teaches dependency on needle gauge, as opposed to the presently claimed invention. As such, the

methods taught in the '618 reference will not result in the maintenance of biological activity, because using a smaller needle gauge would necessitate use of a higher velocity to maintain a predetermined flow rate. Also, '618 is completely silent as to a method for injecting cells.

Applicants assert that the '624 reference teaches an apparatus for delivering drugs into the heart. As set forth in the Abstract:

> "Apparatus for intracardiac drug administration, including a catheter (20, 45, 64) which is inserted into a chamber of the heart and brought into engagement with a site in the heart wall (72). The catheter includes at least one position sensor {32), which generates signals responsive to the position of the catheter within the heart, and a drug delivery device (24, 27), which administers a desired dose of a therapeutic drug at the site determined responsive to the signals from the position sensor."

As set forth in claim 45:

> "A method according to any of claims 34-44, and comprising receiving physiological signals from the heart, wherein administering the therapeutic drug comprises administering the drug responsive to the physiological signal."

The Examiner asserts that claim 45 teaches the modulation of delivery based on physiological signals. However, Applicants respectfully assert that the '624 reference teaches otherwise. For example, page 4, line 29 to page 5, line 5 states:

> "In some preferred embodiments of the present invention, the catheter also includes one or more physiological sensors, for diagnosis and identification of sites in the myocardium that are in need of drug administration. Preferably, the sensors are used to identify ischemic areas in which growth factors are to be administered. Most preferably, the physiological sensors are used in conjunction with the position sensor to produce a viability map of the heart, in accordance with which the drug is administered, as described further herein below.
>
> In some preferred embodiments of the present invention, the catheter is operated in conjunction with a drug dispenser, which meters and dispenses predetermined quantities of the drug, and a control circuit, for controlling and triggering the operation of the apparatus."

As such, the above quoted exemplary portions of '624 clearly teach that the physiological sensors are used to identify ischemic areas in which growth factors are to be administered. Applicants assert that the Examiner has mischaracterized claim 45 and page 5, lines 3-5 teach dispensing drugs in predetermined quantities, and does not teach controlling flow rates or velocities. Thus, the '624 reference does not teach a method of injecting cells to maintain their biological activity by controlling velocity.

Applicants assert that the '604 reference teaches the injection of muscle cells into the heart to aid in cardiac repair. As set forth in the Abstract:

> "Muscle cells and methods for using the muscle cells are provided. In one embodiment, the invention provides transplantable skeletal muscle cell compositions and their methods of use. In one embodiment, the muscle cells can be transplanted into patients having disorders characterized by insufficient cardiac function, e.g., congestive heart failure, in a subject by administering the skeletal myoblasts to the subject. The muscle cells can be autologous, allogenic, or xenogeneic to the recipient."

Applicants assert that the '604 reference does not teach a method of injecting cells to maintain their biological activity by controlling velocity.

Regarding velocity and flow rate, Applicants assert that the present specification interchanges the usage of "flow rate" and "velocity". For example, at page 54, paragraph 3 of the specification, it states:

> "As used herein, the term "velocity" refers to an injection velocity of a liquid drug containing a cell unless otherwise specified. In the present invention, the importance of maintaining a predetermined flow rate unchanged and the effect thereof have been unexpectedly found. The flow rate can be represented by linear velocity. Therefore, it will be understood that the velocity may be represented by linear velocity if particularly specified, though the velocity usually means flow rate."

As noted above, "'velocity' refers to the injection velocity of a liquid drug containing a cell", and that the "'velocity' may be represented by linear velocity... though the 'velocity' usually means flow rate".

With respect to the obviousness rejections, Applicants assert that the MPEP states that to establish a prima facie case of obviousness, three basic criteria must be met.

(1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

(2) There must be a reasonable expectation of success.

(3) The prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure.

Applicants respectfully assert that a *prima facie* case of obviousness has not been properly established. There is no suggestion nor motivation to combine the references based on their own disclosures or common general knowledge of one of ordinary skill in the art based on the teachings therein. There is no reasonable expectation of success that the disclosures of the references would achieve the present invention. Lastly, the references do not teach or suggest all the claim limitations.

Specifically, as described above, '618 teaches the control of flow rates, acceleration and deceleration rates in relation to easing patient discomfort, '624 teaches the delivery of drugs directly to the heart, and '604 teaches the use of skeletal muscle cells to treat cardiac disorders. The alleviation of patient discomfort caused by injection is not discussed or relevant to the administration of drugs or cells to the heart. As such, there would be no motivation to combine any of these references in order to attain the invention, whereby cell injury due to injection is prevented by controlling velocity. Further, '618 specifically teaches that the adjustment of flow rate is dependent on dispensing time as well as the gauge of the needle (refer to excerpt above). This clearly teaches away from the present invention, in which needle gauge is irrelevant in maintaining biological activity of injected cells, as shown on, for example, page 80, lines 15-31 and Example 4 of the present specification. Page 80, lines 15-31 of the present specification states:

> "It was unexpectedly found that the effect of the predetermined range of velocity does not depend on the type of syringe, and substantially not on the inner diameter of a syringe. Therefore, the present invention provides an unexpected

technique in which by maintaining the velocity (i.e., flow rate) of a cell within a predetermined range, the cell can be injected while maintaining the proliferation ability thereof. this phenomenon has not been heretofore reported and is substantially unpredictable from a physical theory. Thus, the effect of the present invention is significant.

Velocity is the only parameter which has an influence on the result. The velocity can be easily adjusted by physicians or medical practitioners with ordinary skill. Therefore, the present invention provides a technique for simply and efficiently injecting cells into the body."

An excerpt from Example 4 of the present specification includes:

"Shafts (tip tubes) having an inner diameter in the range of 0.1 mm to 1 mm were employed,, In each case, velocity as described in Examples 1 and 2 could be achieved. It was found that the inner diameter of the shaft (tip tubes) has substantially no influence on the proliferation rate of a cell. Therefore, it was unexpectedly demonstrated that in the present invention, cells can be injected into organisms substantially irrespective of the inner diameter of a shaft (tip tubes)."

Further, '618 is completely silent as to a method for injecting cells which is another reason as to why there would be no motivation to combine these references. As such, there is no reason why one of ordinary skill in the art would consider using the invention of '618 to inject cells for treatment, let alone to configure it to maintain biological activity.

Thus, it is clear that there would be no motivation to combine any of the references because of the varied fields of technology described in the references, and the dramatically different problem solved by the present invention. Even if one of ordinary skill in the art would choose to somehow combine these particular references for a different reason, there would be no reasonable expectation that one would successfully arrive at the present invention.

Furthermore, the references do not disclose all the claim limitations. Specifically, none of the references, nor any combination thereof, teach the controlling of injection velocities to preserve the biological activity of injected cells. This distinguishable feature of the presently claimed invention is clearly demonstrated in the Examples and Figures in the present specification at, for example, Example 6 which discloses the ability of the present invention to successfully inject a liquid drug containing cells to a target site without impairing the

survivability of the cells.

An excerpt from Example 6 of the present specification includes:

> "Next, a liquid drug injecting device of the present invention was used for treatment using cells. A device as shown in Figure 2 was fabricated. The device was used to carry out a cell injection experiment while adjusting velocity in an experimental system as shown in Example 5.
>
> It was confirmed that the device could adjust the cell injection velocity between 1 ml/min and 20 ml/min. The device was used to carry out an experiment as shown in Example 5. Substantially the same result was obtained. It was confirmed that cells could be actually injected efficiently without impairing the survivability of the cells."

The cited references teach modifying different parameters to achieve different purposes. None of the references, nor any combination thereof, teach predetermined velocities to maintain biological activity of an injected cell, and some teach away from manipulating that parameter. Therefore, even if one skilled in the art were to combine the references, they would not arrive at the present invention. There is no motivation to combine these references because they do not contain the relevant teachings, nor is there any reasonable expectation of success in doing so because of the different problem to be solved.

With respect to claims 6 and 8, namely a predetermined range of acceleration, Applicants assert that the above arguments (with regards to controlling velocity to maintain biological activity by preventing cell damage caused by injection force) can also be extended for arguments for controlling acceleration. The force a cell experiences during injection is directly proportional to the acceleration of the cell. Therefore, limiting the acceleration of the cell would limit the maximum amount of injection force experienced by the cell. Therein, cell injury can be prevented, and biological activity maintained.

Dependent claims 4, 6-10 and 14-16 depend from independent claim 1, so Applicants assert that dependent claims 4, 6-10 and 14-16 are differentiated from the cited references for at least the reasons set forth above, in addition to their own respective features.

New dependent claims 43-59 variously depend from independent claims 1 and 17, so Applicants assert that dependent claims 43-59 are differentiated from the cited references for at least the reasons set forth above, in addition to their own respective features.

In view of the above remarks and amendments, Applicants respectfully submit that all pending claims properly set forth that which Applicants regard as their invention and are allowable over the cited references. Accordingly, Applicants respectfully request allowance of the pending claims. The Examiner is invited to telephone the undersigned at the Examiner's convenience, if that would help further prosecution of the subject Application. Applicants authorize and respectfully request that any fees due be charged to Deposit Account No. 19-2814.

Respectfully submitted,

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